

13 January 1956

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Dr. R. C. Pogge
Director of Medical Research
The Wm. S. Merrell Company
Cincinnati 15, Ohio

Dear Dr. Pogge:

We have completed the effort to reverse the LSD reaction with Frenquel, except for checking the statistical constants. I am enclosing tables which show the results.

The methods used were the same as those described in the report on the "blocking" experiment, with one exception - the kneejerk. This was measured by determining the angle through which a calibrated hammer must fall in order to elicit a detectable kneejerk. Pupils were measured by comparing their diameter with those of circles on a card in a dark room under conditions of constant light. Blood pressure was determined by the auscultatory method after 10 minutes rest in bed. The mental effects of LSD were assessed by administration of our version of the Abramson-Jarvik questionnaire for two hours before and eight hours after administration of LSD and by a short psychiatric examination in which particular attention was paid to anxiety, apprehension, perceptual distortion, hallucinations, and insight was done hourly, and also within a few minutes after administration of Frenquel.

You will recall that in this system Grade 1 consisted of nervousness, anxiety and apprehension only. Grade 2, nervousness, anxiety, apprehension, and visual distortion. Grade 3, anxiety, apprehension, visual distortion, and hallucinations with maintenance of insight. Grade 4, same as Grade 3, but with insight lost.

These observations were all carried out for two hours before and eight hours after LSD. The measurable of "nonmental" effects of LSD are evaluated by plotting the data on graph paper and measuring the area under the time-action curve with a planimeter. Positive answers on questionnaire were counted hourly and totaled for the entire day. Questions which were scored positively prior to LSD were eliminated. Clinical grades were evaluated hourly and for the total day according to the system described above.

A-267
207

We had 12 subjects but lost one of these, since we were unable to get into a vein during one of the LSD experiments. All subjects were negro males and were former opiate addicts. All had had LSD experiences prior to these experiments. None were psychotic.

LSD was given orally. The mean dose was 2.4 micrograms per kilogram. The dose for each individual was set by preliminary experiments and varied between 1.5 to 3 mcg/kg. The object of individual dosage was to obtain Grade 3 reaction in every subject. Two of the patients, however, did not have a Grade 3 reaction, reaching only Grade 1 or 2. LSD placebo was tap water. Frenquel was administered intravenously, 60 mg. being given at two hours after LSD and 40 mg additional given three hours after LSD.

Patients were not told what drug was being studied or what the object of the experiment was. We carefully avoided asking any patient how his sensations compared with those prior to the intravenous injection, or how they compared with the sensations during other weeks. Some patients made spontaneous comments about changes and these were recorded.

Combinations used were LSD placebo plus Frenquel placebo; LSD placebo plus Frenquel; LSD plus Frenquel placebo; and LSD plus Frenquel. All tests were double-blind and the code was not broken until all data had been tabulated and analyzed.

Results are shown in the attached tables. The table on the "Effects of Frenquel in Changing the Total Course of the LSD Reaction" shows the analysis according to our usual system. It is readily apparent that there is no difference between the LSD plus Frenquel placebo and LSD plus Frenquel columns. Another table shows the effects with respect to questions and clinical grade hour-by-hour. Again, no difference is apparent.

The spontaneous comments by the patients were of some interest. Six reported alleviation of anxiety, nervousness, etc, after the first injection of Frenquel placebo; 1 reported his anxiety was worse; and 4 made no comment. Four patients reported alleviation of anxiety and nervousness after Frenquel; 2 were worse; and 6 made no comment (one reported both improvement and worsening).

A-216

Individual analysis of the records from a qualitative point of view hour-by-hour also showed no difference. Hallucinations and perceptual distortion continued to be present after the Frenquel and declined at the usual rate. This point is best exemplified by case report on the patient whom Dr. Allin saw during his visit here.

LSD

December 9, 1955. 150 mcgm/(11.5 mcg/kg) at 8 a.m. At 9 o'clock, nervous, confused, nauseated, body is expanding and contracting, hands and feet look big, eyes are blurred, objects are changing size and shape, skin melts off hands leaving only bones, insects are crawling under his skin, colors on wall running together like melted wax and forming pictures of people and ghosts. Pictures are horrible but not disturbing, because he knows they are due to LSD. 10 o'clock ~~am~~, nervous and apprehensive, confused, feels as if in a nightmare, has been floating in the air, people and objects are changing size, shape and color. He can see blood vessels under the skin, things are crawling under the skin, head is dried up and shrunken, and pictures on the walls are parts of people, animals, devils, and so on. Insight maintained. At 10 a.m. received 60 mg. Frenquel intravenously. After injection, patient reported to the Aide that all LSD effects had disappeared. Dr. Allin and I immediately went to see about this and on detailed questioning found the patient still had marked visual distortion, hallucinations of the type described above, but still maintained insight. At 11 a.m. patient received 40 mg. Frenquel intravenously. He reported nervousness was less, but still was obviously confused, visual distortions in size shape and color were still present, flesh still melted off hands and he could see blood vessels and bones, I looked very small, very small, and very horrible. Insight was still present.

Twelve to 4 a.m. symptoms gradually decreased. At 4 p.m. was still seeing colored lights which, however, formed no definite pictures, continued tense and strange until 2 a.m., after which he went to sleep.

December 30, 1955. At 8 a.m., patient given 150 mcgm LSD (11.5 mcg/kg). At 9 a.m. nervousness, walls are seen through a fog, many lights and colors seen with eyes closed, feet and hands seem to melt, look old and skinny, felt strange, confused and lost. At 10 a.m. still confused, feels strange and lost, orientation is maintained, very nervous, people and objects are changing size, shape and color. His hands and my hands

A-215

decay and turn into animal claws, walls are covered with pictures resembling melted wax, pictures are of ghosts, pretty women and so on, his body has disappeared from the chest down. 10 a.m., given Frenquel placebo. After this, reported he was much more relaxed and LSD effects were less. He was obviously still confused and on looking at the walls still saw the pictures, hands still decay, stomach is gone, effects are due to LSD. 11 a.m. Frenquel placebo was repeated. Pictures still on wall, sees lights and colors with eyes closed, people and objects are very distorted, insight maintained. 12 M to 4 p.m. Effects, which persisted throughout this time, gradually became weaker. At 4 a.m., still saw lights with eyes closed, and nervousness and hallucinations continued until about 2 a.m.

I would be pleased to have your reaction to this. I can conclude only that, in the doses used, Frenquel had no significant effect on the LSD reaction.

I believe that I have told you Reserpine makes the LSD reaction worse, rather than ameliorating it. This means that the effects of a drug on the LSD reaction cannot be used to predict its possible clinical usefulness as a quieting agent in the "natural" psychoses. Our experiments, therefore, have no bearing on the potentialities of Frenquel in these conditions.

I was very interested in Hemmich's report of its use in schizophrenics. If this is confirmed, there can be no doubt that Frenquel would be a very useful agent because of its extremely low toxicity.

With kindest personal regards.

Sincerely yours,

Harris Isbell, M.D.
Director

H:rn

Attachments 3

A-214

EFFECTS OF FRENQUEL IN CHANGING THE TOTAL COURSE OF THE LSD REACTION

Measure	LSD Placebo + Frenquel Placebo	LSD Placebo + Frenquel**	LSD* + Frenquel Placebo	LSD* + Frenquel*
Knee Jerk ¹	+ 0.12	+ 0.60	+ 1.90	+ 1.47
Pupillary Size ¹	+ 0.69	+ 0.69	+ 5.51	+ 5.31
Systolic Blood Pressure	+ 1.61	+ 0.79	+ 3.25	+ 3.32
No. of Positive Answers on Questionnaire ²	5	6	79	87
Clinical Grade ³	0.1	0.2	+ 2.8	+ 2.7

Figures are means of values on 11 subjects. None of the differences between LSD + Frenquel placebo or LSD + Frenquel are significant.

1. Expressed as square inches under effect curve, 8 a.m. - 4 p.m.
 2. Number of answers on questionnaires, excluding any that were also scored positively before LSD.
 3. Based on scale of 1-4 (see text).
- * Dose 1.5 - 3.0 mg/kg. Average 2.4.
- ** Dose 60 mg. i.v. 2 hours and 40 mg. i.v. 3 hours after LSD.

4-213

EFFECTS OF FRENQUEL IN CHANGING LSD REACTION HOUR-BY-HOUR

DRUGS		HOUR AFTER LSD							
		1	2	3	4	5	6	7	8
POSITIVE ANSWERS	LSD-placebo + Frenquel-Placebo	1	1	1	1	1	0	0	0
	LSD-placebo + Frenquel	1	1	1	1	1	0	0	0
	LSD + Frenquel Placebo	11	18	16	13	9	5	4	3
	LSD + Frenquel	15	18	17	13	8	6	5	5
CLINICAL GRADE	LSD-placebo + Frenquel-Placebo	0.1	0.1	0.1	0	0	0	0	0
	LSD-placebo + Frenquel	0.1	0.1	0.2	0.2	0	0	0	0
	LSD + Frenquel Placebo	2.2	2.7	2.8	2.3	1.5	1	0.7	0.7
	LSD + Frenquel	2.4	2.7	2.7	2.4	2.1	1.6	0.9	0.9

Figures are means on 11 patients. Mean dose of LSD 2.4 mcg/kg. Dose of Frenquel 60 mg. i.v. 2 hours and 40 mg. i.v. ^{three hours} after LSD.

A-2/2

SPONTANEOUS COMMENTS ON FRENQUEL

	FRENQUEL A	FRENQUEL B
[REDACTED]	↓	0
[REDACTED]	-	0
[REDACTED]	0	-
[REDACTED]	0	↓
[REDACTED]	0	0
[REDACTED]	0	0
[REDACTED]		-
[REDACTED]	↓	↓
[REDACTED]	↓	0
[REDACTED]	↓ (?)	↓
[REDACTED]	↓	↓
[REDACTED]	↓ (?)	
	6 4 1	4 6 2 (One man reported both ways)

A-211